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1,3 - Dipolar Cycloaddition Reactions of 1-Aza-1-Cyclooctene 1-oxide

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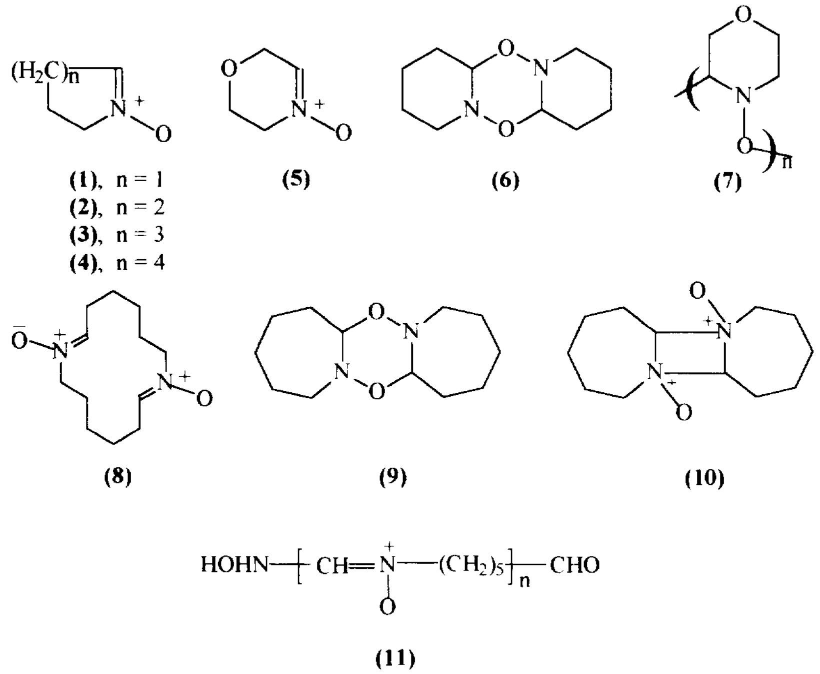
***Abstract*:** The stereochemistry and reactivity of the cycloaddition reactions of eight-membered cyclic nitrone (**4**) with several alkenes have been studied. The concentrated solution of the cyclic nitrone undergoes polymerization to give acyclic polynitrone (**15**). The nitrone **4** is found to be less reactive than its seven-membered counterpart. Barrier to nitrogen inversion in one of the cycloaddition product, a 8/5 fused ring system, was determined to be 55.4 kJ/mol. © 1997 Elsevier Science Ltd.

Introduction

The 1,3-dipolar cycloaddition reaction of nitrones has become an important chemical tool in organic synthesis.[1] Remarkable regio- and stereo-selectivity along with efficient incorporation of multiple stereocentres have made nitrone cycloaddition an attractive key step in the synthesis of a variety of natural products of biological interest. Both cyclic (five-, six- and seven-membered)[2] (**1**) - (**3**), (**5**) and acyclic nitrones[1] have been studied in some detail (scheme 1). The cyclic nitrones which can exist only in *E* isomeric form, because of geometric constraints, are found to under go addition reactions with higher stereoselection and faster rate[3] than their acyclic counterparts where *E*⇔*Z* isomerization is possible with equilibrium favouring the more stable *Z* form.

Behaviour of concentrated solutions of the cyclic nitrones is quite puzzling. While the nitrone (**1**) is stable, the nitrone (**2**) dimerizes to (**6**) and the nitrone (**5**) polymerizes[4] to (**7**) with a repeating skeletal of -N-O-C- unit. The seven-membered ring nitrone (**3**), on the other hand, quite interestingly dimerizes[5] to the fourteen-membered cyclic dinitrone (**8**) (scheme 1). It is suggested that the structural reorganization of dimer **9** through **10** would lead to the dinitrone **8** which then undergoes further polymerization by ring expansion to trimer, tetramer etc. until a trace of moisture causes hydrolysis of a nitrone group leading to the linear polymer **11**. To the best of our knowledge preparation and characterisation of the eight-membered ring nitrone (**4**) and its addition reactions are not reported to date. It would indeed be interesting to investigate the polymerization behaviour (if any) of this nitrone.

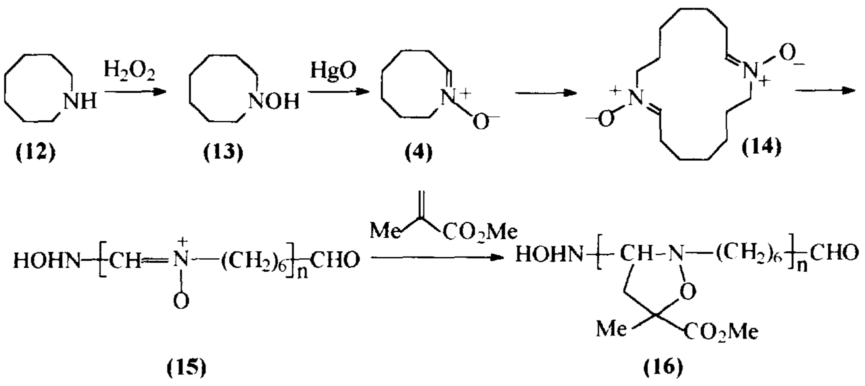


Scheme 1.

Herein we report, in some detail, the effects of ring size on the regio- and stereo-chemical features along with reactivity phenomena associated with the addition reactions of the nitrone (**4**). We also examined the slow nitrogen inversion in one of the resulting cycloaddition products, the isoxazolidines.

Results and Discussion

At the outset the preparation of the nitrone **4** posed a problem. The experimental procedure as described in the literature for the preparation of **4** by SeO_2 mediated oxidation of heptamethyleneimine (**12**) using hydrogen peroxide was re-examined[6] several times. Each time a mixture of products along with polymeric materials were obtained. However, mercury(II) oxide oxidation of the hydroxylamine (**13**), obtained by oxidation of the amine **12** with H_2O_2, afforded the nitrone in almost quantitative yield (scheme 2). The C(2) olefinic and C(8) protons of the nitrone appeared at δ 7.15 and 4.03 ppm respectively, as expected. When ^{1}H NMR spectrum of a 1.10 M solution of the nitrone **4** in $CDCl_3$ at 26°C was recorded at several intervals, there appeared two new triplets in the olefinic region at δ 6.81 and 6.74 ppm. With the



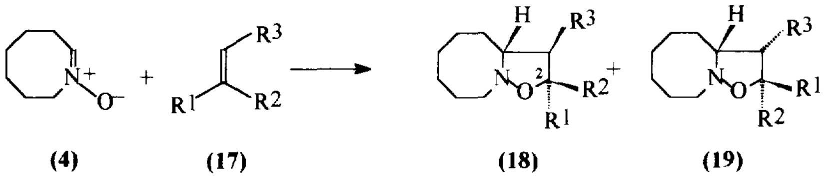
Scheme 2.

passage of time the intensity of the upfield signal at δ 6.74 ppm increased at the expense of the signal at δ 7.15 for the nitrone **4**. At the end of 80 h there remained only the up field triplets at 6.74 ppm, the other two triplets almost disappeared. The sharp triplet at δ 6.81 ppm is assigned to the dimeric nitrone, presumably having the *E* configuration of the nitrone functionality as depicted in **14**. The *Z* nitrone **4** with the *cis* disposition of oxygen and olefinic hydrogen is known to resonate[7] at lower field. We attempted to determine the rate of disappearance of the monomeric nitrone **4** (M).

$$-d(M)/dt = k[M]^2 + k'[M][D] + k''[M][T] + \text{etc.}$$

The rate equation is complicated due to various terms that describe addition of the mononitrone to itself and to the resulting dinitrone (**D**) and to the trinitrone (**T**). However, at the early stages of the process, the first term of the polynomial will dominate the rate equation. The second order rate constant k, obtained by linear regression analysis, was found to be 2.77×10^{-5} L mol^{-1} s^{-1} and as expected the rate increased progressively in the latter stages of the reaction due to the impact of the other terms in the polynomial.

The dilute solutions of the monomeric nitrone **4** in dichloromethane at 0°C remained stable. However, after stripping of the solvent the nitrone polymerized immediately to white amorphous solid. Careful analysis of the NMR spectrum of this solid revealed a minor signal at δ 9.80 ppm indicating the presence of aldehyde end group. Integration of the aldehyde and alkene signals of the polynitrone (**15**) indicated the degree of polymerization as 50. Earlier report[6] on the synthesis of the mononitrone **4** is doubtful, presumably they obtained the linear polynitrone **15** in the process of isolation. The presence of nitrone functionality in polynitrone **15** was demonstrated by its addition onto methyl methacrylate to give polyadduct **16** in almost quantitative yield (scheme 2). As before the NMR spectrum revealed the presence of the aldehyde end group and the degree of polymerization as 45.



a, $R^1 = R^3 = H$, $R^2 = Ph$
b, $R^1 = R^3 = H$, $R^2 = OEt$
c, $R^1 = CO_2Me$, $R^2 = Me$, $R^3 = H$
d, $R^1 = H$, $R^2 = R^3 = CO_2Me$
e, $R^1 = H$, $R^2, R^3 = (CO)_2O$

Scheme 3.

Next we pursued the addition reaction of the mononitrone **4** for the first time. The concentration of the nitrone and alkene was kept low and high, respectively, in order to minimise polymerization of the nitrone. The stereochemical details along with isolated yields for these addition reactions are included in Table 1. The additions of styrene, methyl methacrylate and ethyl vinyl ether were found to be regiospecific with oxygen of the nitrone functionality attaching itself to the more substituted end of the alkenes as expected[1] (scheme 3). Based on precedent literature[2] the major adduct was assigned the configuration as

Table 1: Stereochemistry of cycloaddition of nitrone **4** with alkenes.

alkene	composition of adducts		isolated yield
(17)	**(18)**	**(19)**	(%)
(a)	91	9	86
(b)	88	12	70
(c)	95	5	73
(d)	60	40	69
(e)	30	70	77

depicted in **18** with *exo*-orientation of the phenyl group in **18a** and ethoxy in **18b** obtained *via* sterically favoured *exo*-mode of attack.

The addition of methyl methacrylate was found to be highly regio- as well as stereo-selective; - the formation of the adduct (**18c**) with *endo* orientation of the methoxycarbonyl amply demonstrate the importance of favourable secondary orbital interaction in dictating stereoselection.[2]

Interplay of steric encumbrance and favourable secondary orbital interaction is demonstrated in the addition reactions of dimethyl maleate and maleic anhydride with the nitrone (**4**). While the former alkene afforded the major adduct (**18d**) with *exo* disposition of methoxycarbonyl groups, maleic anhydride gave the *endo* oriented adduct (**19e**) as the major product. Maleic anhydride, being less sterically demanding than the dimethyl maleate, is able to manifest favourable secondary orbital interaction and over-ride the steric factor present in the *endo* transition state. The configuration of maleic anhydride adducts (**18e**, **19e**) was correlated to dimethyl maleate adducts (**18d**, **19d**) by chemical conversion, using methanol-HCl. The assignment of configuration of the adducts was based on the reasonable assumption that maleic anhydride due to its smaller size should give a higher proportion of the *endo* oriented adducts.

Table 2: Rate constants and activation parameters for the cycloaddition reaction of the nitrone **4** in $CDCl_3$

Alkene	Temp/ °C	$k_2/10^{-5}$ $dm^3mol^{-1}s^{-1}$	E_a/ kJ mol^{-1}	$\Delta H^{\#}$/ kJ mol^{-1}	$\Delta G^{\#}$/ kJ mol^{-1}	$\Delta S^{\#}$/ J $mol^{-1}K^{-1}$
Methyl acrylate	16	70.5	52.7	50.2	89.3	-131
	26	155				
	36	290				
Methyl methacrylate	16	52.1	48.5	46.0	90.6	-148
	26	93.9				
	36	193				
Dimethyl maleate	36	70.2				

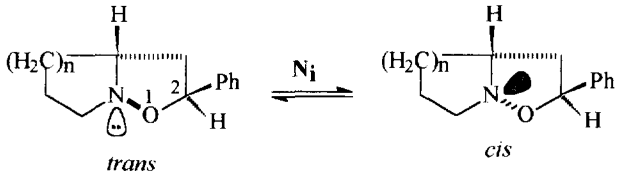
Measurement of rate constants for the addition of the nitrone **4** on several alkenes was achieved using ^1H NMR technique. Cycloadditions were monitored at different temperatures by the disappearance of ^1H nmr signals of C(2)H signal of the nitrone and olefinic protons of the alkenes. The ratio of the nitrone and alkene was determined from time to time and the second order rate constants were obtained by linear regression analysis. The kinetic results obtained for the cycloaddition in $CDCl_3$ are shown in Table 2. Low activation energies and large negative entropies of activation reflect the concerted nature of the multicentered cycloaddition reactions. It is evident from Table 2 that methyl acrylate is the most reactive among the three alkenes studied. Steric factors play an important role in deciding the rate of addition reactions. Crowded transition state with *cis* disposition of the methoxycarbonyl groups makes dimethyl maleate the least reactive.

The ratio of the rate constant at 36°C for the addition of the seven-membered[3b] (**3**) and eight-membered nitrone (**4**) with methyl acrylate, methyl methacrylate and dimethyl maleate was found to be 1.56, 2.11 and 2.17, respectively. Thus with all three alkenes the nitrone **4** is less reactive than its seven-membered counterpart **3**. For medium size rings larger than six-membered, angle strain plays a minor part but eclipsing strain[8] is introduced as the hybridization of the atoms in the imine part of the nitrone functionality changes its hybridization from sp^2 to sp^3. Cyclooctane is known to have greater eclipsing strain than cycloheptane[9] and as such non-bonded repulsions are expected to be unfavourable in the transition state leading to the 8-5 ring system. This could account for the slower rate of addition of the cyclic nitrone **4**.

Finally, we decided to investigate the stereochemistry of the ring junction of the cycloaddition product. Slow nitrogen inversion provides the required avenue to such study. ^1H nmr spectrum of the styrene adduct (**18a**) at room temperature showed the benzylic proton as a triplet at 5.00 ppm (*J* 7.4 Hz). However, at lower temperatures the spectra showed the presence of two isomers as indicated by the presence of two kinds of benzylic proton signals at δ 4.91 (dd, *J* 6.1, 9.1 Hz) and 5.07 (dd, *J* 4.7, 9.8 Hz) in a respective ratio of 3:1.

To measure the barrier to nitrogen inversion, the coalescence temperature method could not be used as the populations for the two exchanging sites are widely different. Hence, a complete band-shape analysis corresponding to a non-coupled two-site exchange with unequal populations was employed.[10] The C(2)-H protons offered convenient signals to study the band shapes with variable temperature, as these signals were far away from any overlapping signals and show only first order couplings. Obtaining accurate exchange rate constants by fitting NMR band shapes is well known[11] to be fraught with difficulties, and to have considerable errors in thermodynamic parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ if Eyring plots are used. In fact many errors are systematic in nature, and those resulting from $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are often mutually compensatory so that $\Delta G^{\neq}$ is better defined near coalescence temperature. The $\Delta G^{\neq}$ for the nitrogen inversion for the isomerization of the major to minor isomer of **18a** was determined to be 55.4 kJ/mol. For the purpose of comparison the inversion barriers[12] for the corresponding styrene adducts (**20**) - (**22**) from the nitrones (**1**) - (**3**) are included in Table 3. Barriers in **22** (7/5 fused) and **18** (8/5 fused) are found to be similar but lower than that in **21** (6/5 fused) by an amount of almost 15 kJ/mol. Due to geometric constraints the *cis* form remains the sole isomer in 5/5 system and as such nitrogen inversion barrier in **20** can not be determined. The difficulty in nitrogen inversion in **21** can be attributed to the sp^2 hybridized planar transition state with extended CNC angle of 120° which transforms the ground state chair form of the six-membered ring towards energetically unfavourable half chair form. In analogy[12] with the 6/5 and 7/5 systems the major isomer of the present 8/5 compound **18a** was assigned the *trans* configuration. The benzylic proton of the *trans* isomers in all three cases appears upfield, presumably the *cis* disposition of the nitrogen lone pair with the benzylic proton causes this shielding.

Table 3: Nitrogen inversion barriers and isomer ratios of cycloadducts **18, 20 - 22**



Adducts	*trans*:*cis*[a]	$\Delta G^{\#}$ (kJ mol^{-1})
(**20**), n = 1	~0:100	-
(**21**), n = 2	78:22	68.1
(**22**), n = 3	81:19	54.3
(**18**), n = 4	75:25	55.4

[a] in $CDCl_3$ at ~ -40 °C.

At this stage we are unable to offer rationale for the puzzling differences in the behaviour of the concentrated solutions of the cyclic nitrones. Isolation and trapping of the elusive dimeric nitrone **14** is currently under investigation. Cycloadditions of the eight-membered nitrone **4** have indeed paved the way to incorporate and elaborate the medium size ring systems.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Nicolet 5 DBX FT IR and are reported in wave numbers (cm^{-1}). The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-200 and a Jeol GX 270 NMR spectrometers operating at a proton frequency of 200.0 and 270.0 MHz, respectively using deutereochloroform as solvent and TMS as internal standard. Variable temperature NMR spectra were recorded using XL-200 variable temperature accessory and the temperatures were calibrated using standard chemical shifts of methanol at low temperatures. Mass spectra at 70 ev E.I. were recorded on a Ribermag GC-MS system, R-10-10 with quadrupole mass filter and Riber 400 acquisition system. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analyser. Cycloaddition reactions were carried out under a positive atmosphere of nitrogen. Silica gel chromatographic separations were performed with flash silica (Baker Chemical Co.). All solvents were reagent grade.

N-hydroxyheptamethyleneimine (13).- The N-hydroxyheptamethyleneimine was prepared using procedure of Thesing and Meyer[13] through oxidation of heptamethyleneimine (**12**) with 30% H_2O_2 and was obtained as a colourless liquid (20%), b.p.$_{8\text{-}10\ mmHg}$ 107-110°C, (Found: C,64.9; H, 11.55; N, 10.7. $C_7H_{15}NO$ requires C, 65.07; H, 11.70; N, 10.84%); $\nu_{max.}$ (neat) 3240, 2940, 2864, 1663, 1448, 1362, 1295, 1252, 1113, 1032, 991, 964, 946, 907, 897, and 781 cm^{-1}; δ_H 1.28-1.92(10 H, m), 3.13 (4 H, app.t, *J* 6.5 Hz), 8.70 (1 H, br).

1-Aza-1-cyclooctene 1-oxide (4).- To a solution of N-hydroxyheptamethyleneimine (**13**) (4.27 g, 33.0 mmol) in CH_2Cl_2 (150 cm^3) at 0 °C was added yellow mercuric oxide (15.0 g, 69.3 mmol) in three portion over a period of 15 min. Within minutes after HgO addition, the reaction mixture became grayish. Stirring was continued for an additional 0.5 h at 0 °C. After the completion of the reaction, (as indicated by TLC experiment in ether) it was filtered through a bed of $MgSO_4$ and washed with cold CH_2Cl_2. The total volume of the solution was 275 cm^3 and thus the concentration of the nitrone was 0.12 M. The formation of the nitrone (**4**) was assumed to be quantitative in the percent yield calculation for the subsequent cycloadditions. The nitrone solution in dichloromethane was kept in the freezer in order to avoid any polymerization. In order to record the ^1H and ^{13}C spectra of the nitrone, the hydroxylamine (**13**) (50 mg) was oxidized with HgO in $CDCl_3$ (1 cm^3) as above. After filtration through a small bed of MgSO4 the spectra were recorded. δ_H 1.52-1.84 (6 H, m), 2.02 (2 H,m), 2.40 (2 H, m), 4.03 (2 H app.t, *J* 6.5 Hz), 7.15 (1H, t, *J* 8.0 Hz); δ_C 24.0, 26.2, 28.1, 28.4, 29.9, 57.7, 139.0.

Polymerization of the nitrone (4).- The polymerization of a 1.10 M solution of the nitrone (**4**) in $CDCl_3$ at 26°C was studied as described in Results and Discussion. Following are the molarity (M) of the unreacted nitrone (**4**) with time written in parenthesis: 1.10 M (0 h); 0.969 M (1 h 17 min); 0.769 M (3 h 44 min); 0.524 M (7 h 10 min); 0.391 M (11 h 18 min); 0.0937 M (28 h 52 min); 0.0722 M (33 h 25 min); 0.0319 M (50 h 20 min); 0 M (80 h).

A solution of the nitrone (**4**) in CH_2Cl_2 was left overnight in a beaker for slow evaporation at 20°C. The residue was triturated with ether and the white amorphous powder was washed with liberal excess of ether. The polymer (**15**) does not have a proper melting point up to 350°C. It started to become brownish at around 180°C and became black at the end (350°C) without melting. (Found: C, 65.9; H, 10.35; N, 10.9. $(C_7H_{13}NO)_n$ requires C, 66.10; H, 10.30; N, 11.02%); $\nu_{max.}$ (KBr) 3415, 3088, 3026, 2939, 2858, 1606, 1460, 1428, 1197, 1118, 1055, 917 cm^{-1}; δ_H 1.12-1.77(6 H, m), 1.91 (2 H, m), 2.49 (2 H, app. q, *J* 6.5 Hz), 3.75 (2 H, t, *J* 6.5 Hz), 6.74 (1 H, br t, *J* 5.5 Hz); δ_C 25.3, 26.0, 26.4, 27.2, 28.9, 65.2, 139.2.

Cycloaddition Reaction of the Polynitrone (15) with Methyl Methacrylate.- To a mixture of the polynitrone (**15**) (100 mg) in chloroform (2 cm^3) was added methyl methacrylate (0.7 cm^3) and heated at 55°C for 48 h. After removal of the solvent and excess alkene the product (**16**) was obtained as a pale yellow liquid in almost quantitative yield. $\nu_{max.}$ (neat) 2936, 2872, 1735, 1457, 1372, 1299, 1201, 1162, 1143, 989, 946, 828, 753, 732 cm^{-1}; δ_H 1.00-2.00 (13 H, m including methyl singlets at 1.47 and 1.50 ppm), 2.08-3.00 (5 H, m), 3.75 (3 H, overlapping singlets).

Isomers of 2-Phenyl-1-oxa-11-azabicyclo[6,3,0]undecane (18a), (19a).- A solution of the nitrone (**4**) (3.0 mmol) in dichloromethane (25 cm^3) and styrene (2.0 cm^3) was refluxed for 24 h. The crude reaction mixture after removal of the solvent and excess styrene was purified by chromatography over silica gel using hexane-ether (9:1) mixture as the eluant to give a mixture of the adducts (**18a**) and (**19a**) followed by pure isomer (**18a**) as a colourless liquid (598 mg, 86%). (Found: C, 77.9; H, 9.05; N, 6.0. $C_{15}H_{21}NO$ requires C, 77.88, H, 9.15; N,6.06%); $\nu_{max.}$ (KBr) 3030, 2926, 2849, 1595, 1452, 1384, 1353, 1330, 1281,1160, 1156, 1129, 1114, 1088, 1060, 1031, 1004, 988, 941, 906, 899, 758, and 697 cm^{-1}; δ_H (+27 °C, major isomer) 1.20-2.00 (9 H, m), 2.35 (3 H, m), 2.90 (1 H, m), 3.24 (1 H, m), 3.42 (1 H, m), 5.00 (1 H, t, *J* 7.4 Hz), and 7.36 (5 H, m); *m/z* 231(M^+ 79.9%), 127(56.9), 104(100); ^1H NMR at -50 °C displayed the C(2) H signals at δ 4.91 (0.75 x 1H, dd, *J* 6.1, 9.1 Hz) and δ 5.07 (0.25 x 1H, dd, *J* 4.7, 9.8 Hz). The ratio of the two isomers (**18a**) and (**19a**) was found to be 91 : 9, respectively, as determined by integration of C(2) H NMR signals of the crude reaction mixture, which revealed the presence of a minor dd (*J* 4.0, 10.0 Hz) at δ 5.06 assigned to the C(2) H of the minor isomer (**19a**)

Isomers of 2-Ethoxy-1-oxa-11-azabicyclo[6,3,0]undecane (18b), (19b).- A solution of the nitrone (**4**) (2.4 mmol) and ethyl vinyl ether (2 cm^3) in dichloromethane (20 cm^3) was heated at 57°C for 18 h in a closed vessel. After removal of the solvent and excess alkene, the residual liquid was chromatographed on silica gel using (95:5) mixture of hexane/ether as the eluant to give a mixture of adducts (**18b**) and (**19b**) (230 mg, 48.1%) followed by the pure compound (**18b**) (107 mg, 22.3%) as a colorless liquid. The ratio of the isomer (**18b**) and (**19b**) was estimated by the integration of the C(2)H signals and was found to be 88 : 12 respectively. (Found: C, 66.2; H, 10.5; N, 6.9. $C_{11}H_{21}NO_2$ requires C, 66.29; H, 10.62; N, 7.03%); $\nu_{max.}$ (neat) 2982, 2920, 2852, 1456, 1444, 1402, 1370, 1357, 1339, 1239, 1195, 1171, 1157, 1139, 1113, 1083, 1045, 1031, 992, 973, 957, 940, 861; δ_H (+25°C, major isomer) 1.14, (3 H, t, *J* 7.0 Hz), 1.37 (3 H, m) , 1.52-1.88 (7 H, m) 1.95 (1 H, dt , *J* 5.0, 12.0 Hz), 2.40 (1 H, dd, *J* 7.0, 12.0 Hz), 2.92 (1 H, m), 3.26 (1 H, m) 3.41 (2 H, m), 3.74 (1 H, dq, *J* 7.0, 9.9 Hz), 4.94 (1 H, d, *J* 4.8 Hz). The C(2) H of the minor isomer (**19b**) appeared at δ 5.02 as dd (*J* 3.0, 6.0 Hz).

Isomers of Methyl 2-methyl-1-oxa-11-azabicyclo [6,3,0,]undecane-2-carboxylate (18c), (19c).- A solution of the nitrone (**4**) (3.0 mmol) and methyl methacrylate (2 cm^3) in dichloromethane (25 cm^3) was stirred at 20°C for 6h. After removal of the solvent and excess alkene, chromatographic purification of the product residue with 4:1 mixture as eluant on silica gel yielded the adduct (**18c**) followed by a mixture of the adducts (**18c**) and (**19c**) as a colourless liquid. (Found: C,63.2; H, 9.15; N, 6.0. $C_{12}H_{21}NO_3$ requires C, 63.41; H, 9.31; N, 6.16%) (497 mg, 73%); $\nu_{max.}$ (neat) 2955, 2931, 2859, 1735, 1455, 1371, 1298, 1264, 1255, 1203, 1166, 1139, 1096, 1062, 989, 950, 735 cm^{-1}; δ_H (+25°C, major isomer) 1.20-1.95 (9 H, m), 1.48 (3 H, s), 2.23 (2 H, m), 2.58 (1 H, m), 2.83 (1 H, m) 3.06 (1 H, m), 3.48 (1 H, m) , 3.77 (3 H, s). The NMR spectrum of the crude mixture displayed a minor singlet at δ1.53 ppm assigned to the C(2) methyl protons of the minor isomer (**19c**). The ratio of the isomers was estimated from the peak height of the C(2) methyl singlets.

Isomers of *cis*-Dimethyl 1-oxa-11-azabicylo [6.3.0] undecane-2,3-dicarboxylate (18d),(19d) .- A solution of the nitrone (**4**) (2.4 mmol) and dimethyl maleate (2.0 cm^3) in dichloromethane (20 cm^3) was stirred at 57°C in a close vessel for 6 h. After removal of the solvent the residue on chromatographic purification with 4:1 mixture hexane-ether as eluant gave the major isomer (**18d**) as a white solid (272 mg, 41.7%). Continued elution afforded the minor isomer (**19d**) as a white solid (178 mg, 27.3%). The ratio of the major and minor isomer was found to be 60:40 which was supported by the NMR integration of the C(2) proton signals. Major isomer (**18d**): Cottony crystals, m.p. 82-83 °C (ether-hexane) (Found: C, 57.4; H, 7.7; N, 5.0. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N, 5.16%); *m z* 271 (M^+ 4.3%), ν_{max} (neat) 3002, 2917, 2875, 1768, 1736, 1478, 1452, 1362, 1280, 1234, 1208, 1183, 1056, 935, 867; δ_H (+25°C) 1.20-2.08 (10 H, m), 3.00 (1 H, m) 3.38 (2 H, m), 3.72 (3 H, s), 3.75 (3 H, s and 1 H, m underneath the methyl singlet), 4.68 (1 H, d, *J* 7.8 Hz). Minor isomer (**19d**): Cottony crystals, m.p. 85 - 86 °C (ether-hexane) (Found: C, 57.35; H, 7.6; N, 5.1. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N, 5.16%); ν_{max} (neat) 2946, 2856, 1736, 1438, 1382, 1300, 1246, 1192, 1164, 1106, 1036, 1016, 982, 904, 808; δ_H (+25°C) 1.28-1.90 (10 H, m), 2.00 (1 H, m), 3.44 (2 H, m),3.72 (3 H, s), 3.78 (3 H, s), 3.80 (1 H, m), 4.98 (1 H, d, *J* 7.6 Hz).

Reaction of the Nitrone (4) with Maleic Anhydride.- Reaction of the nitrone (**4**) with maleic anhydride in dichloromethane initially gave adducts which converted slowly to unknown insoluble material. In another trial maleic anhydride (0.60 mmol) was added to a solution of nitrone (0.50 mmol) in $CDCl_3$ (1.5 cm^3) in an NMR tube at 20°C for 10 min. The NMR spectrum revealed the presence of the two adducts (**18e**) and (**19e**) in a ratio of 30 : 70, respectively as determined by the integration of C(2) H signal at δ 4.93 (d, *J* 8.0 Hz) for the minor isomer and δ 4.98 (d, *J* 8.0 Hz) for the major isomer. To the above reaction mixture after removal of the solvent, 2.0 ml of a mixture of methanolic-HCl (3:2 w/w) at 20°C was added and allowed to stand for 48 h. After removal of the excess methanol the residue was taken up in saturated K_2CO_3 solution and extracted with ether (3 x 20 cm^3). The organic layer was dried ($MgSO_4$) and purified by silica gel chromatography (as describe before in the case of dimethyl maleate adducts) to give the adducts (**18d**) and (**19d**) (isolated yield 104 mg, 77%) in an approximate ratio of 30:70, respectively.

Kinetics of Cycloaddition Reaction.- The nitrone for kinetic runs was prepared by HgO oxidation of the hydroxylamine (**13**) in $CDCl_3$ at 0°C. The stock solution of the nitrone **4** was kept in the refrigerator. Kinetic runs were studied in NMR tube as described in our earlier works.[3] The concentration of the nitrone was kept low (between 0.1 - 0.3 M) in order to eliminate polymerization process. The ratio of the concentration of the reactants was determined from time to time by integration of the signals due to C(2)H of the nitrone and the olefinic proton of the alkene. The second order rate constant was determined by linear regression analysis of the data and was reproducible within 5%. The additions were followed up to 60 - 80% of the chemical conversion. The initial concentration, written in parenthesis, of the nitrone (**4**) and alkenes for some of the kinetic runs were as follows: nitrone (0.121 M) - methyl acrylate (0.182 M); nitrone (0.287 M) - methylmethacyrlate (0.392 M); nitrone (0.230 M) - dimethylmaleate (0.726 M).

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